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# Blood Transfusion Services

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## Definitions and Approaches

'Blood' is a fluid tissue, composed from various cells with complex functions (erythrocytes, red cells – oxygen carriers; leucocytes, white cells – immune response to disease; and thrombocytes – cytoplasmic fragments of larger cells/megakaryocytes, activated when bleeding occurs), which are carried by plasma (over 90% water, plus proteins, minerals, etc.). Blood is vital as carrying oxygen, nutrients, and other essential elements to the tissues and removing residues of cellular metabolism. It also carries various clotting factors which normally intervene when bleeding occurs.

'Blood donation' is a benevolent gesture of offering blood for patients in need. Every healthy individual 18–65 years of age can donate blood, about 7 ml per kg body weight, up to a maximum of 450 ml whole blood per donation. To ensure donor availability, some countries have lowered the donation age to 17 and allowed blood donation after 65 years of age, if all donor health criteria are fulfilled. The interval between two whole blood donations has to be at least 72 days. Voluntary nonremunerated blood donation is considered a cornerstone of blood safety and it is advocated and supported by many international bodies, such as World Health Organization, the International Federation of Red Cross and Red Crescent Societies, the International Federation of Blood Donor Organizations, and the International Society for Blood Transfusion (see Relevant Websites).

'Blood transfusion' is a medical treatment in which donated blood (collected and prepared from a healthy person – a donor) is administered to the patient being treated, in the form of blood components, blood derivatives, or in rare and very specific situations as whole blood. The most appropriate blood transfusion therapy should provide for the missing or reduced element. Transfusion of whole blood can be lifesaving in situations such as massive blood loss due to trauma, burns, or extensive surgery. Blood component therapy is used to treat conditions in which the specific element is missing; for example, packed red cell administration in the case of severe anemia (a reduction in oxygen supply to vital organs) or platelet concentrates transfused for an abnormal decrease in the number of platelets. People suffering from sickle-cell disease may require frequent transfusion of red cell concentrates. In the case of hemophilia, the administration of the missing clotting factor (Factor VIII or IX concentrate or alternative recombinants) is required. Blood transfusion treatment is usually performed in health-care settings.

'Blood transfusion service' deals with various aspects of the blood transfusion chain, from the potential donor (information and selection of donors, blood collection, blood testing, blood processing, blood storage, blood transportation) to the potential recipient (selection and distribution of appropriate components for transfusion), and should link to the clinical interface and patient follow-up. It is important to note that donor promotion and awareness to blood donation is also part of blood service activities. This complex work is usually carried out by dedicated organizations/institutions or departments that operate at national, regional, or local level. In some countries blood services are hospital based. The range of responsibilities of the blood services (hospital or nonhospital based) varies, according to the organization of the national health-care system. Usually, the hospital blood service is a transfusion department that bears the responsibilities of storage, selection (compatibility testing), and administration of blood components according to medical prescription.

'Blood components' result from the separation of collected whole blood through centrifugation at various speeds. Components include red cells, white cells, thrombocytes, and plasma. Each component has specific characteristics, including a special storage temperature and shelf life (e.g., thrombocytes must be stored at +21 °C; plasma must be frozen at −40 °C). The time between preparation and storage has direct consequences on the quality of active factors in the respective unit for transfusion or fractionation. Blood components can also be collected from the individual donor through apheresis procedures (separation of the required component from collected blood during the donation procedure, with the remaining being returned to the donor at the end of the separation process). The procedure can be fully or partially automated.

'Blood derivatives' are obtained through industrial fractionation procedures from raw plasma. These procedures must follow the pharmaceutical current good manufacturing practices (cGMP) so that resulting products comply with required safety standards. The purified and concentrated coagulation factors (e.g., Factor VIII, Factor IX), human albumin (usually prepared as 5% or 20% solutions), and immune globulins are the most frequently used blood derivatives.

Technological progress has been achieved in developing pharmacologic alternatives to transfusion therapy, which include volume replacement solutions and plasma expanders, recombinant coagulation factors, erythropoiesis (red cell production) stimulation factors, in the continuous strive to cover patients' therapeutic needs and identify measures addressing an insufficient blood supply, increasingly exposed to safety threats. To further respond to blood availability challenges, increasing attention is given to the development of blood substitutes and oxygen carriers.

## Safety Aspects of Blood Transfusion

Being a complex but undeniable life source, blood has been given historically mythical attributes. After unsuccessful transfusions of blood from animals to humans, and sometimes from humans to humans as well, it was only after 1900, when Karl Landsteiner discovered the ABO major blood groups, that blood transfusion therapy became possible. The

history of blood transfusion has shown that once the blood group compatibility barrier had been overcome, there are infectious threats to which increased attention must be given. (For a more comprehensive overview of the history of blood transfusion, see Starr, 1998.) Blood-borne pathogens can be transferred with the donor's blood to the recipient patient. Such pathogens may be viruses (e.g., HIV/AIDS, hepatitis B and C), parasites (e.g., malaria, Chagas' disease), bacteria (e.g., syphilis, brucellosis), or prions (e.g., vCJD).

In the late 1980s the transmission of the HIV by blood, blood components, and by pharmaceutically manufactured blood derivatives raised important concerns. A large number of patients chronically depending on therapy with blood components or derivatives were proven to be infected with HIV and other blood-borne pathogens. These findings led to more firm regulations of the entire blood transfusion area, with patient protection being of central importance. Other crisis situations, such as the variant Creutzfeldt–Jakob disease (vCJD) infections (mad cow disease), severe acute respiratory syndrome, avian flu epidemics, seasonal malaria and West Nile virus transmission, and the recent Ebola virus outbreak, have strongly affected the availability of the national blood supplies at times.

Climate change and increased cross-border movement have led to revised geographical distributions of emerging and reemerging pathogens transmittable through blood. Extensive screening of donors and donations, and postprocessing treatment of blood products (including pathogen inactivation technologies) became part of the quality management and quality assurance operations. A nonexhaustive list of infectious agents which can be transmitted by blood transfusion is presented in Table 1. These agents in their early stage of infection may induce a healthy carrier state with few or no symptoms of disease. It is important to note that even if this list is under continuous development and scrutiny, not all agents are being tested for each donation. As of today, mandatory testing of blood donations concerns HIV-1, -2; hepatitis B and C viruses; and syphilis, to which locally significant testing requirements are added. By locally significant, in context, one should understand the local epidemiology (incidence and prevalence of specific infections in the populations) and links with its seasonal variations when applicable. Considering the limitations of testing procedures (infections are not identified during their initial phase – window period, new infectious agents for which tests have not been developed, quality of tests, and testing algorithm in place), the appropriate selection of potential blood donors should be given its full importance in maintaining safe blood supplies.

The public and political attention focused on the infectious safety risks, led to more sophisticated and numerous testing procedures, and increasingly complex donor selection criteria. This placed on the second line the noninfectious safety concerns that become today in the high and medium human development index (HDI) countries, the leading causes of transfusion-related incidents and adverse events. Of physical (such as volume overload) or immunologic causality (such as allergic reactions, hemolytic reactions, transfusion-related acute lung injury, graft-versus-host disease), the intrinsic mechanisms of noninfectious safety risks related to blood transfusion including immune modulation require close monitoring, and some are still being explored. Hence, the vital importance of ABO/D blood grouping, and extended compatibility testing, required for every unit to be transfused. A nonexhaustive list of noninfectious hazards related to blood transfusion is presented in Table 2.

**Table 1** Nonexhaustive list of infectious agents that (can) adversely affect the availability and safety of blood supplies

| *Infectious agent* | *Observations* |
|---|---|
| **Viruses** | |
| Influenza viruses | Major impact on donor availability, to date no published reports of transmission of influenza viruses through transfusion |
| Hepatitis viruses: A, B, C, D, E | Hepatitis B and C viruses are part of the basic mandatory screening of donors and donated blood |
| Herpesviruses: Epstein–Barr virus, human cytomegalovirus, human herpesvirus 8 | With particular relevance for transfusion in patients with reduced immune protection capacity (neonates, conditions associated with immune deficiency) |
| Retroviruses: human immunodeficiency virus (HIV-1 and HIV-2), human T cell lymphotrophic virus (HTLV-I and HTLV-II) | HIV-1 and HIV-2 are part of the basic mandatory screening of donors and donated blood HIV1 (with three genetic groups, nine known subtypes and recombinants) accounts for over 90% of HIV infections worldwide |
| Erythroviruses: parvovirus B19 | Documented transmission through transfusion of untreated pooled components and organ transplantation |
| Mosquito-borne viruses: West Nile virus (WNV), chikungunya virus, dengue virus | Increasing geographic spread in recent decades, mandatory seasonal testing for WNV introduced in affected areas |
| **Bacteria** | |
| *Treponema pallidum* | Syphilis, part of the basic mandatory screening of donors and donated blood |
| *Borrelia burgdorferi* | Lyme disease |
| *Brucella melitensis* | Brucellosis |
| *Coxiella burnetii* | Q fever |
| **Parasites** | |
| Plasmodium species: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* | Malaria, reemergence due to climate change in recent years, donor deferral policies and available immunological testing |
| *Trypanosoma cruzi* | Chagas' disease |
| *Toxoplasma gondii* | Toxoplasmosis |
| *Leishmania donovani* | Leishmaniosis |
| *Babesia microti* | Babesiosis |
| **Nonconventional agents** | |
| Prions | Variant Creutzfeldt–Jakob disease |

## Present Situation

The safety, availability of and access to adequate blood supplies are still challenged in many parts of the world.

**Table 2** Nonexhaustive list of noninfectious risks related to blood transfusion

| *Condition* | *Notes* |
|---|---|
| **Immunologic mechanisms** | |
| **Acute occurrence** | |
| ● Allergic reactions | Different degrees of severity (mild febrile and chills, urticarial reactions, anaphylaxis); recipient antibodies to donor plasma proteins |
| ● Hemloytic reactions | Red cell incompatibility (ABO/D blood groups), recipient irregular antibodies to donor erythrocytes antigens |
| ● White blood cell incompatibility | Recipient antibodies against HLA antigenic system on donor white cells |
| ● Transfusion-related lung injury (TRALI) | Severe and potentially lethal complication, transfusion of all blood components reported to be involved in TRALI (high level of specific antibodies in donor/donation involved) |
| **Delayed occurrence** | |
| ● Alloimunization | Antibodies anti-RBC and HLA antigens developed in patient, with impact on future administration of blood components |
| ● Graft-versus-host disease | Severe but rare complication, donor antibodies (T lymphocytes) target recipient tissues, occurring in patients with immune deficiency |
| ● Posttransfusion purpura | Recipient developing antiplatelet antibodies, with resulting thrombocytopenia |
| **Nonimmunologic mechanisms** | |
| **Acute occurrence** | |
| ● Circulatory overload | Follows rapid or massive transfusion (large quantities of fluids) |
| ● Hemolytic reactions | Related to storage length and quality of the transfused product |
| ● Metabolic disturbances | Acute hypotensive reactions, hypothermia, metabolic alkalosis in massive transfusions, hyperkalemia, hypocalcemia |
| **Delayed occurrence** | |
| ● Iron overload | In patients subject to chronic transfusions (i.e., major thalassemia patients) |
| ● Metabolic disturbances | Delayed hypoglycemia following exchange transfusion |

According to the latest WHO global database for blood safety summary report, drawing from 2008 data reported by 164 countries, an estimate of 91.8 million blood donations are collected annually (WHO GDBS Summary report, 2011). Analysis of blood donations in relation to the HDI showed that almost half of these blood donations are collected in high-income countries. 85% of the world's population, which lives in low and medium HDI countries, has access to only 52% of the total blood supply. This has a dramatic impact on the capacity to respond to various health needs of the population, and the strong links between blood availability and maternal mortality rates have been demonstrated.

The differences in blood donation rates (that globally range between 0.4 and 64.6 per 1000 population) reflect not only the degree of awareness and involvement of the population with respect to blood donation and blood transfusion (local culture and health education) but also the level of development of health care in which the blood service is embedded. With mounting safety requirements and technological progress, blood transfusion services have become an increasingly expensive component of public health. In countries with limited resources, the safety of blood transfusion is of particular concern. In addition to the gaps in terms of technological progress available in the field, there are often high prevalence rates of HIV, hepatitis B and C, and other particular blood-borne diseases (see Relevant Websites of WHO, CDC). There is no generic formula for the calculation of what an appropriate blood supply would mean in size and constituency, and a relative value is usually calculated for planning purposes, based on retrospective analysis of covered and actual patient unmet needs in transfusion therapy. An appropriate blood supply can be defined as a situation in which no patient will die due to lack of appropriate treatment with blood, blood components, and/or blood derivatives and subsequently varies from one country to another. The sequence of steps undertaken to collect, produce, and administer a therapeutic blood unit is presented in a simplified manner in **Figure 1**.

## Essentials in Blood Safety

Important components of blood safety are:

- Organization, coordination, and regulatory framework for the blood transfusion services;
- Safe blood donors – education, recruitment, screening, retention, and medical follow-up;
- Safe blood units – collection, testing, further processing, and storage;
- Safe transfusion therapy – appropriate use of blood and blood components at the clinical site;
- Hemovigilance – reporting and follow-up on safety issues and transfusion outcomes.

WHO promotes an integrated strategy for blood transfusion safety, recommending (1) national coordination of specialized services to ensure that harmonized practices, safety standards, and quality management systems are uniformly applied in all areas, (2) regular voluntary nonremunerated blood donors from low-risk populations as primary source for the national blood supply, (3) appropriately tested (for blood-borne pathogens, blood grouping, and compatibility testing), processed, stored, distributed, and (4) adequately used at the hospital site including postdonation and posttransfusion follow-up for donor and recipient respectively. Preventive measures to reduce transfusion therapy needs and use, including availability of alternatives to transfusion, are part of enforcing strategies for blood supply management. A 15% increase in national blood policy development, with overall 58% countries having specific legislation in place for 2008 was reported to the WHO Global Database on Blood safety (Summary report, 2011).

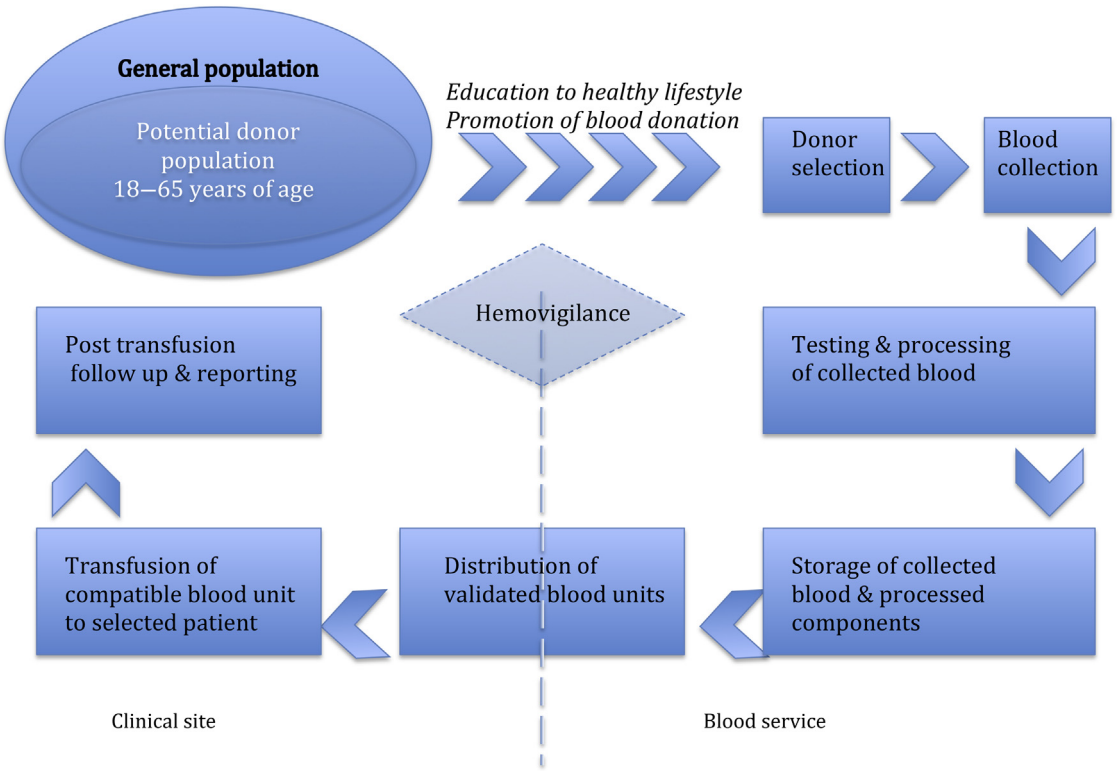


**Figure 1** Simplified flow of the blood donation and transfusion process.

## Organization and Supportive Frameworks for the Blood Transfusion Services

The blood transfusion service should be integrated with the health-care system of a country. Its appropriateness depends on the strength of public health interventions, the development level of health service delivery (preventive and curative medicine), and the health status of the population it serves. Experience has shown that the organization of blood services on a nationally coordinated basis ensures harmonized quality standards along the blood chain and increases consistency in delivery of products, information, and statistics. In addition, such organization has been proven to be more cost-effective owing to economies of scale.

The blood transfusion service usually functions under government responsibility. A national blood policy and plan should define the vision and the steps required for strengthening quality, safety, availability, and access to adequate blood supplies. A national blood program for defined periods of time will allow addressing priorities and monitoring progress in the field. Constantly updated, dedicated, legal provisions and regulatory frameworks are part of the supportive mechanisms to implementation. Appropriate resources, including sustainable funding mechanisms, are needed for its appropriate functioning.

The blood service organization and functioning should be looked at horizontally bridging the involvement of the various stakeholders and related interventions. A dedicated national commission with mixed representation can play an advisory function at a high decision-making level with respect to blood safety issues, as well as enhance dialog among interested parties, such as blood transfusion specialists, clinicians, and patients.

National Regulatory Authorities have the mandate to evaluate and monitor compliance of blood service operations with agreed quality standards, and the way supportive quality management systems ensure that products meet the standards in use. Quality and safety standards for the blood services operations are grounded in more general standards, such as the ISO 9000-series standards and the cGMP guidelines for medicinal products for human and veterinary use. Resulting from concerted efforts and combined expertise of national experts and international organizations, these common standards are subject to periodic review to ensure they keep pace with advances in science and technology development, and adequately respond to safety challenges and patient needs. Monitoring the compliance to defined standards is part of a regular process of quality assessment and control.

## Safe Blood Donors

According to data available from various sources and studies, voluntary nonremunerated regular blood donors recruited from low-risk populations carry a much lower risk of infections. Safe donor selection criteria, which reflect the education to healthy lifestyles, proved to be highly effective in the prevention of HIV/AIDS transmission. The 'Club 25' initiative in Africa (youth initiative promoting lifestyles and regular blood donation, aiming for about 20 blood donations by

the age of 25) led to a dramatic decrease in transfusion-transmitted infections and related risks, to the mutual benefit of donors and recipient patients. The safe blood donors are the cornerstone of a safe blood supply and therefore an important and central point in WHO recommendations as well as other international organizations concerned.

Establishing a pool of safe blood donors requires long-term commitments to education, information, and social involvement. Efforts in this respect have been particularly enhanced with the World Blood Donor Day, launched in 2004, and endorsed by the World Health Assembly in 2005 as global annual event. Cosponsored by WHO, the International Federation of Red Cross and Red Crescent Societies (IFRCRCS), International Federation of Blood Donor Organizations (IFBDO/FIODS), and International Society of Blood Transfusion (ISBT), it aims to increase awareness toward blood donation and enhance the different steps in the process of education, recruitment, and retention of low-risk donors and establishment of youth donor programs. The theme of World Blood Donor Day 2014 was dedicated to safe motherhood.

In the current epidemiological context (i.e., blood safety potential threats) and extended cross-border movement, donor selection criteria have become more stringent with the aim to reduce residual risks. There is a constant debate on how far the donor screening and selection procedures should go, considering their impact on actual donor availability, blood supplies, and patient safety.

The Melbourne declaration on 100% voluntary nonremunerated blood donation of blood and blood components (2009) and the Rome declaration on achieving self-sufficiency in safe blood and blood products based on voluntary nonremunerated blood donations (2013) emphasize the vital importance of safe blood donations (i.e., voluntary nonremunerated) in preserving adequate and sustainable national blood supplies and healthy populations.

## Testing and Processing of Blood

Collected blood needs to be screened for blood-borne pathogens prior to transfusion. Basic screening includes tests for HIV, hepatitis B, hepatitis C, and syphilis. In some parts of the world, additional tests are necessary for local epidemiological threats. It is the responsibility of health authorities to outline a national strategy for screening of all donated blood and specify the most appropriate testing and diagnostic algorithms to be used. In addition, testing for ABO and RhD blood groups, as well as screening for irregular antibodies, is performed to avoid an incompatible (hemolytic) transfusion reaction.

Reliable testing of blood units requires the following:

1. Uninterrupted supply of high-quality test systems; this includes procurement, supply, central storage, and distribution of reagents and materials to ensure continuity of testing;
2. Maintenance of a quality assurance system and good laboratory practice, including the use of standard operating procedures for all aspects of blood screening and processing;
3. Continuous training of staff members in all aspects of blood screening and processing of blood units, including storage and transportation of blood products.

Collected whole blood can be stored for a time depending on the mixture of anticoagulant preservation solution used. The whole blood unit may be separated into major blood components – packed red cell, fresh frozen plasma, and platelet concentrate – to increase efficiency of use. Processing of donated blood into its different components reduces the occurrence of adverse transfusion reactions and tailors therapeutic response to the particular needs of the patient. Since each blood component can be stored according to its specific requirements, effectiveness is increased and shelf-life adjusted. Time interval between collection, separation, and storage at the correct temperature also influences the quality and expected transfusion efficiency of the separated component. In what fresh frozen plasma is concerned, separation should be done within 6 h from collection and at not more than 18 h if refrigerated. Separated plasma should be subject to fast freezing (less than 1 h) at below −30 °C. Fresh frozen plasma can be stored at −40 °C for 36 months, pooled platelets suspended can be stored at +20 to 24 °C for 3–5 and up to 7 days depending on the suspension media, and red cells suspended in an additive solution (SAG-MAN or ADSOL) can be used up to 45 days if stored at +4 °C.

Raw plasma for industrial fractionation (obtained from separated whole blood donations or apheresis procedures) has to comply to specific quality and safety requirements and is subject to standardized testing, industrial processing (extraction and purification) following pharmaceutical GMP and results in several individualized protein fractions, such as Factor VIII, IX concentrates; albumin and immune globulins (most frequently produced).

Considering the life saving role of transfusion therapy when needed, blood components and blood derivatives have been recently included in the WHO list of essential medicines.

## Appropriate Clinical Use of Blood

Blood is a scarce resource and should always be used with care. As with any medical procedure, it carries also a measurable risk to the recipient patient. In evaluating the indication for blood transfusion therapy, the benefits for the patient should outweigh the risks. Several international recommendations and guidelines have been developed in this respect, but these are not always available or used, and in many circumstances the process continues to rest on historically based practices and the clinical experience of the attending physicians. Several studies have shown important differences in usage of blood transfusion therapy within and between countries, for similar clinical pathologies.

The training of clinical users in the adequate use of blood is an important endeavor which requires constant updates not only regarding scientific progress and technologies but also the availability of and access to alternatives to transfusion therapy (pharmaceutical products, clinical prevention, and procedures). Strengthening the collaboration and coordination with different levels of health care may help reduce blood usage through (1) prevention and education to health; (2) early diagnosis and treatment of diseases or conditions which may lead to the need for blood transfusion (obstetric antenatal care, iron substitution, etc.); (3) use of evidence-based latest therapeutic guidelines and microinvasive/bloodless surgical technologies;

(4) replacement therapies where applicable (preoperative blood collection for autotransfusion; intraoperative normovolemic hemodilution; preoperative and postoperative blood salvage). Optimization of therapeutic blood usage is required not only by the scarcity of this natural reserve but also on maintaining an appropriate balance between related risks and benefits.

In recent years, the concept of patient blood management (PBM), based on the earlier enumerated principles for reducing the clinical use of blood, has gained more and more attention and adherence in the clinical community of mainly high and medium HDI. The three pillars of PBM focus on optimization of red cell mass, reduction of blood loss/bleeding and optimization of the physiological reserve of anemia (see Isbister, 2013). Explaining the benefits and risks of transfusion therapies to patients and families is an important element in creating the necessary understanding of this apparently simple procedure. An informed patient will be knowledgeable of the residual risks related to the transfusion if given (no zero risk), as well as be involved in the informed choice of alternatives. The expert patient will be equally able to observe if safety steps such as appropriate identification, skin disinfection, etc., are followed and contribute to reducing the potential occurrence of transfusion-related hazards.

The Network for Advancement of Patient Blood Management, Haemostasis and Thrombosis collects and promotes evidence-based interventions supporting these concepts, altogether with several (inter)national initiatives and web-based platforms for information exchange.

### Hemovigilance

'Hemovigilance,' 'pharmacovigilance,' and 'materiovigilance' find their application in blood transfusion safety, as a set of complementary surveillance ('vigilance') procedures covering the whole transfusion chain (from the collection of blood and its components to the follow-up of the transfused patient), to monitor, record, and analyze occurring deviations to quality and safety standards and practices, and their impact on donor safety, patient safety, or health-care worker safety.

The aim of hemovigilance is to collect all information of unexpected, undesirable, or serious adverse events in donors or in patient recipients of blood transfusion therapy in order to correct their cause, prevent recurrence, and improve the safety of blood collection and transfusion. It also looks into donor epidemiological follow-up, as part of organized surveillance procedures. Adverse reactions are defined as reactions which are unintended and occur during collection or transfusion procedures.

Reporting of serious adverse events related to transfusion therapy appears to be one of the oldest reporting systems in place. However, the development of national hemovigilance systems poses increasing challenges. These relate to how hemovigilance is regulated in terms of accountability and responsibilities for reporting donation/transfusion-related events, to the various taxonomies in use and how the degree of severity and the reporting trigger are defined, the limited resources for supportive information technologies, and, mainly, the communication between blood services and hospital services (reporting, route cause analysis of reported events and feedback).

Several websites provide data on hemovigilance (national and regional). The International Haemovigilance Network (formed in 2009) collects information from national operational hemovigilance systems and provides a forum for shared information and best practices in the field. Drawing from collected data, IHN has developed the International Surveillance of Transfusion Associated Reactions and Events (ISTARE) that can be used for benchmarking as well as monitoring progress and trends. Hemovigilance is to be seen as a safety tool fostering reporting and learning. The increasing role of the patient in this process is expected to strengthen hemovigilance at its operational level.

*See also:* Brucellosis; Hepatitis, Viral; History of Malaria and Its Control; HIV/AIDS and Tuberculosis; Lyme Disease; Protozoan Diseases: Malaria Clinical Features, Management, and Prevention; Protozoan Diseases: Toxoplasmosis; Social Dimensions of Epidemics.

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## Relevant Websites

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http://www.redcross.org/ – American Red Cross.

http://www.edqm.eu/ – European Directorate for the Quality of Medicines & HealthCare, Council of Europe.
http://www.eur-lex.europa.eu/ – EUR-Lex.
http://www.fiods.org/ – International Federation of Blood Donor Organizations.
http://www.ifrc.org/ – International Federation of Red Cross and Red Crescent Societies.
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http://www.nataonline.com/ – Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis.
http://www.thalassaemia.org.cy/ – Thalassemia International Federation.
http://www.wfh.or/ – World Federation of Haemophilia.
http://www.who.int/bloodsafety/ – World Health Organization: Blood Transfusion Safety.